=> d l3 5,6 kwic

US PAT NO: 5,389,675 [IMAGE AVAILABLE] L3: 5 of 8

SUMMARY:

BSUM(8)

The . . . formed from nitric oxide and primary amines, and esters, ethers or other derivatives of the resulting adducts. These compounds spontaneously **release** **nitric** **oxide** in vivo, and it is this release which accounts for their biological activity. While these nitric oxide-nucleophile complexes have been found to exhibit biological activity through their **release** of **nitric** **oxide**, novel derivatives of these nitric oxide-nucleophile complexes which also **release** **nitric** **oxide** and which exhibit improved potency and/or stability would also be beneficial.

DETDESC:

DETD(7)

The . . . centers which are, in turn, bound to one or more additional ligands. The compounds of this invention are capable of **releasing** **nitric** **oxide**. The compositions in accordance with the invention have the formula:

DETDESC:

DETD(23)

While . . . unsaturated such that donor atoms in mammalian tissue may bind to vacant sites in the coordination sphere of the metal. **Release** of **nitric** **oxide** from the metal complex is thus increased at the target tissue with consequent improvement in response.

DETDESC:

DETD(77)

The . . . toxemia of pregnancy and acute congestive heart failure. The compositions may be administered by any suitable route, e.g., by injection, **inhalation**, and oral administration. The preferred method of administration is by injection into the blood system, most preferably by intravenous injection. . . .

SUMMARY:

BSUM(3)

Since . . . See Parratt, J. R., J. Pharm. Pharmacol., 31, 801 (1979). The utility of these compounds arises from their ability to **release** **nitric** **oxide** (NO). See Ignarro, L. J., Pharmaceutical Research 6, 651 (1989). NO is believed to activate a soluble form of guanylate. . .

SUMMARY:

BSUM(35)

The . . . chronic myocardial ischemia, congestive heart failure and angina pectoris, may be treated sublingually, orally, rectally, vaginally, transdermally, parenterally or by **inhalation**. Other conditions in which the compounds formula (I) have utility include the treatment of Prinzmetal's angina, essential hypertension and pulmonary. . .

SUMMARY:

BSUM(36)

The . . . the patient undergoing the treatment, and is ultimately at the discretion of the physician. However, a suitable oral, sublingual or **inhalation** dose for a mammal, including a human, is in the range of from about 0.01 mg to about 1.5 mg. . .

SUMMARY:

BSUM(37)

The desired daily oral, sublingual or **inhalation** dose is preferably presented as one to about six sub-doses administered at appropriate intervals throughout the day as needed. A. . . syrup, lozenge, suspension or other oral formulation known in the art. Multi-dose pressurized or dry powder dispensers are preferred for **inhalation** with each sub-dose being about 5 to about 10 mg of active compound.

SUMMARY:

BSUM(48)

For administration by **inhalation** or sublingual aerosol, the

compounds of formula (I) are conveniently delivered in the form of an aerosol spray presentation from multi-dose pressurized packs, with a suitable propellant or, for **inhalation**, from a nebulizer. In the case of a pressurized aerosol, the dosage unit may be determined by a metering valve.

SUMMARY:

BSUM(49)

Alternatively, for administration by **inhalation** or insufflation, the compounds of formula (I) may take the form of a dry powder composition, e.g., a powder mixture. . .
=> d l4 4 kwic

US PAT NO: 5,217,997 [IMAGE AVAILABLE] L4: 4 of 4

DETDESC:

DETD(11)

Bronchial asthma is a reversible obstructive **lung** disorder characterized by increased responsiveness of the airways. Bronchial asthma attacks are characterized by narrowing of large and small airways. . . the perpetuation of the abnormal airway responses (late-phase reaction) is only now being appreciated. Airways obstruction causes hypoventilation in some **lung** areas, and continued blood flow to these area leads to a ventilation/perfusion imbalance resulting in hypoxema. Arterial hypoxemia is almost. . . early in the attack. As the attack progresses, the patient's capacity to compensate by hyperventilation of unobstructed areas of the **lung** is further impaired by more extensive airways narrowing and muscular fatigue. Arterial hypoxema worsens and can lead to respiratory acidosis.

DETDESC:

DETD(23)

The . . . rats have a diminished endothelial-dependent relaxation response and that L-arginine may be the physiological precursor of the most powerful endothelial-derived **releasing** factor, **nitric** **oxide**, may suggest that administration of L-arginine to spontaneous hypertensive rats increases the formation of nitric oxide and contributes to an. . .
=> d l3 5,6 cit

5. 5,389,675, Feb. 14, 1995, Mixed ligand metal complexes of nitric

oxide-nucleophile adducts useful as cardiovascular agents; Danae D. Christodoulou, et al., 514/492, 494, 499, 906, 929; 556/45, 113, 130 [IMAGE AVAILABLE]

6. 5,187,305, Feb. 16, 1993, S-nitroso-N-alkonoylpenicillamines; Stephen A. Thompson, et al., 560/145; 556/413, 427 [IMAGE AVAILABLE]

=> d l4 4 cit

4. 5,217,997, Jun. 8, 1993, Use of L-arginine in the treatment of hypertension and other vascular disorders; Richard D. Levere, et al., 514/565 [IMAGE AVAILABLE]

=

36. 5,028,627, Jul. 2, 1991, Method of using arginine derivatives to inhibit systemic hypotension associated with nitric oxide production or endothelial derived relaxing factor; Robert G. Kilbourn, et al., 514/565; 424/85.1, 85.2, 85.5; 514/12, 930 [IMAGE AVAILABLE]

37. 4,954,526, Sep. 4, 1990, Stabilized nitric oxide - primary amine complexes useful as cardiovascular agents; Larry K. Keefer, 514/611, 149, 558, 563, 564, 610; 564/112, 113 [IMAGE AVAILABLE]

=> d l5 36,37 kwic

US PAT NO: 5,028,627 [IMAGE AVAILABLE] L5: 36 of 37

SUMMARY:

BSUM(4)

In . . . endothelial cells, which line blood vessels, can be stimulated to release a substance which relaxes vascular smooth muscle i.e., causes **vasodilatation**. Since the chemical nature of this substance was completely unknown, it was simply named endothelium-derived relaxing factor (DRF). It is now widely accepted that many naturally-occuring substances which act as physiological **vasodilators** mediate all or part of their action by stimulating release of EDRF; these substances include, acetylcholine, histamine, bradykinin, leukotrienes, ADP,. . .

SUMMARY:

BSUM(5)

Other . . . it appeared that: 1) endothelial cell NO generation may be stimulated by similar stimuli and 2) septic shock (i.e., systemic **vasodilatation** induced by bacterial endotoxin) may result from massive activation of NO biosynthesis. Speculation that the latter hypothesis was correct was. . .

DETDESC:

DETD(32)

L-N.sup.G . . . via EDRF/NO release. FIG. 8 shows concentration-response curves for relaxation of guinea pig pulmonary artery rings by endothelium-dependent and endothelium-independent **vasodilators** and the effect of L-N.sup.G -methylarginine (NMA). Vascular rings were preconstricted with 1 uM norepinephrine and relaxation was elicited by. . .

DETDESC:

DETD(33)

NMA blocks the action of ACh, LTD4 and HIST, agents which **vasodilate** by eliciting release of endothelium-derived relaxing factor (EDRF), whereas NMA does not inhibit **vasodilatation** by SNP (which acts directly on vascular smooth muscle). Thus, NMA has a specific action on EDRF-mediated **vasodilatation**. It is noteworthy that L-arginine restored relaxation in the presence of L-NMA and that the D-stereoisomer was not an inhibitor. . .

DETDESC:

DETD(37)

L-NMA . . . cells grown in culture (FIG. 12) and from the isolated guinea pig heart (FIG. 13) when challenged with an endothelium-dependent **vasodilator**.

DETDESC:

DETD(38)

FIG. . . . (L-NMA) of calcium ionophore stimulated nitrite release from bovine aortic endothelial cells grown in cell culture. Cells were stimulated to **release** **nitric** **oxide** by addition of 3 ug/ml of ionophore (A23187) to the culture medium, alone, and in the presence of various concentrations. . .

DETDESC:

DETD(39)

FIG. . . . was determined. Bars represent mean values.+-.SEM (n=4-6). Not shown here is that histamine elicits a dose-dependent increase in coronary flow (**vasodilation**) which is attenuated by L-NMA, but restored by addition of excess L-arginine. Thus, it appears that nitric oxide synthesis from L-arginine mediates, at least in part, histamine-induced coronary artery **vasodilatation** in the guinea pig heart.

DETDESC:

DETD(44)

It . . . in a wide variety of in vitro preparations, from an array of species. Nitric oxide is an important mediator of **vasodilation** in vivo and probably plays an important role in vascular homeostasis. Finally, N.sup.G -substituted arginine analogs may be used as. . .

US PAT NO: 4,954,526 [IMAGE AVAILABLE] L5: 37 of 37

SUMMARY:

BSUM(2)

Numerous . . . and nitric oxide has been postulated to be identical to endothelium-derived relaxing factor (EDRF) which mediates the action of some **vasodilators**, R.M.J. Palmer, et al., Nature, Vol. 327, p. 524-526 (1987), as well as certain types of intercellular communication in the. . .

SUMMARY:

BSUM(4)

One . . . and esters, ethers, or other derivatives thereof. These nitric oxide-primary amine complexes and esters, ethers or other derivatives regenerate, i.e., **release**, **nitric** **oxide** in vivo, and it is this **release** of **nitric** **oxide** in vivo which accounts for their potent biological activity. Furthermore, since the release rate of nitric oxide from nitric oxide-nucleophile. . . pH, and other factors such as temperature, a second object of the present invention is to provide stabilized complexes of **nitric** **oxide** which **release** **nitric** **oxide** in vivo in an acceptable fashion (as determined by pharmacological testing). A third object of the present invention is to. . .

SUMMARY:

BSUM(44)

The compounds of Formula I are stable nitric oxide-primary amine complexes and their esters, both of which generally **release** **nitric** **oxide** in vivo in a controlled fashion. This controlled **release** of **nitric** **oxide** makes the compounds valuable as pharmaceutical agents; and the same compounds are fully contemplated herein as useful in the treatment. . .

SUMMARY:

BSUM(100)

Certain . . . their activity as cardiovascular agents. Inasmuch as the compounds, pharmacological activity, disclosed herein, is related principally to their ability to **release** **nitric** **oxide** in vivo, the following Examples should not be considered limiting to the number of compounds, disclosed herein, which are useful. . . to effectively treat certain cardiovascular disorders such as hypertension, arteriosclerosis, cerebral vasospasm and coronary vasospasm, by way of a controlled **release** of **nitric** **oxide** in vivo.

DETDESC:

DETD(23)

When . . . herein in Example 1, it is predictable that a similar reduction in blood pressure will occur, due to in vivo **release** of **nitric** **oxide** by the Formula I compounds utilized.

```
=> d his
     (FILE 'USPAT' ENTERED AT 10:18:43 ON 24 JUN 1997)
L1            98 S RELEAS? (2A) (NITRIC (1W) OXIDE)
L2            94 S RELEAS? (1A) (NITRIC (1W) OXIDE)
L3            24 S L2 AND LUNG?
L4             0 S L2 AND HYERTENSION
L5            37 S L2 AND VASODILAT?
=
```

```
=> s 514/957,958/ccls
            61 514/957/CCLS
            46 514/958/CCLS
L1         100 514/957,958/CCLS
                ((514/957 OR 514/958)/CCLS)
=> s l1 and nitric (1w) oxide
         41329 NITRIC
        284061 OXIDE
          2503 NITRIC (1W) OXIDE
L2           1 L1 AND NITRIC (1W) OXIDE
=> d l2 1 cit

1.  5,427,797, Jun. 27, 1995, Systemic effects of **nitric** **oxide**
inhalation; Claes G. Frostell, et al., 424/434, 44, 45; 514/826, **957**
[IMAGE AVAILABLE]
=> s 424/434/ccls
L3         186 424/434/CCLS
=> sl l3 and nitric (1w) oxide
'SL' IS NOT A RECOGNIZED COMMAND
=> s l3 and nitric (1w) oxide
         41329 NITRIC
        284061 OXIDE
          2503 NITRIC (1W) OXIDE
L4           4 L3 AND NITRIC (1W) OXIDE
=> d l4 1-4 cit

1.  5,595,753, Jan. 21, 1997, Topical formulations and methods for
treating hemorrhoidal pain and sphincter and smooth muscle spasm in the
gastrointestinal tract; Herbert B. Hechtman, 424/436, **434**, 440;
514/551, 565, 616, 621 [IMAGE AVAILABLE]

2.  5,585,106, Dec. 17, 1996, Particle induced amplification of immune
response; Anthony G. Gristina, et al., 424/401, 45, 85.1, 85.2, 426,
**434**, 435, 445, 489, 499, 501; 514/885; 604/21; 623/16, 18 [IMAGE
AVAILABLE]

3.  5,571,524, Nov. 5, 1996, Agent for curing ischemic myocardial
disease; Masafumi Kitakaze, et al., 424/423, **434**, 435, 451, 464, 489;
514/46, 47, 48 [IMAGE AVAILABLE]

4.  5,427,797, Jun. 27, 1995, Systemic effects of **nitric** **oxide**
inhalation; Claes G. Frostell, et al., **424/434**, 44, 45; 514/826, 957
[IMAGE AVAILABLE]
=> d l2 1 kwic

US PAT NO:     5,427,797 [IMAGE AVAILABLE]            L2: 1 of 1
```

TITLE: Systemic effects of **nitric** **oxide** inhalation
US-CL-CURRENT: 424/434, 44, 45; 514/826, **957**

ABSTRACT:
Nitric **oxide** or **nitric** **oxide** releasing or delivering compounds administered by the inhalation route to humans and animals in need thereof have a systemic and. . .

SUMMARY:

BSUM(2)

Under physiologic conditions, **nitric** **oxide** (NO) is exceedingly unstable, reacting essentially instantaneously with oxygen, superoxide anion, and redox metals (Lancaster et al., Proc. Natl. Acad.. . .

SUMMARY:

BSUM(3)

The . . . inactivation of NO, thus allegedly eliminating any beneficial pharmacological effect. (Furchgott R. F. et al., I. Endothelium-Derived Relaxing Factors and **Nitric** **Oxide**; eds. Rubanyi G. M., pp. (1990); Gryglewski, R. J. et al., Nature 320:454-456 (1986)). Furthermore, NO.sup..multidot. reacts with the redox. . .

SUMMARY:

BSUM(4)

Nonetheless, . . . a method for treating or preventing bronchoconstriction, e.g., asthma or reversible pulmonary vasoconstriction, e.g., pulmonary hypertension, by inhalation of gaseous **nitric** **oxide** or **nitric** **oxide**-releasing compounds. Many such compounds are known. These investigators characterize the mammalian circulatory system as consisting of two separate circuits, the. . .

SUMMARY:

BSUM(6)

In accordance with the present invention, it has been discovered for the first time that **nitric** **oxide** and its adducts, conjugates and other **nitric** **oxide** containing compounds widen administered by the inhalation route to an individual in need thereof, as the compound per se or as part of an adduct, conjugate or the like that releases **nitric** **oxide** (or an alternative redox form of nitrogen monoxide) are

effective to prevent or treat both systemic and pulmonary emboli, effect. . .

DETDESC:

DETD(2)

Thus, . . . a therapeutically effective amount of a compound (or pharmaceutical composition comprising such a compound) selected from the group consisting of **nitric** **oxide** and a compound that releases an effective amount of **nitric** **oxide** upon such administration.

DETDESC:

DETD(3)

Another . . . a therapeutically effective amount of a compound (or pharmaceutical composition comprising such a compound) selected from the group consisting of **nitric** **oxide** and a compound that releases an effective amount of **nitric** **oxide** upon such administration.

DETDESC:

DETD(4)

Another . . . a therapeutically effective amount of a compound (or pharmaceutical composition comprising such a compound) selected from the group consisting of **nitric** **oxide** and a compound that releases an effective amount of **nitric** **oxide** upon such administration. The therapeutic effect in this aspect is realized as a result of the fact that increased pressure. . .

DETDESC:

DETD(5)

Nitric **oxide** releasing or delivering compounds which are useful in the methods of the invention include, but are not limited to, S-nitrosothiols. . .

DETDESC:

DETD(8)

An additional embodiment of the invention relates to the methods of the invention in which the **nitric** **oxide**-delivering compound is administered as part of a pharmaceutical composition, comprising a

pharmaceutically acceptable carrier.

DETDESC:

DETD(9)

Administration of the **nitric** **oxide** or **nitric** **oxide** releasing agent to the lung can be by hand held, portable ventilator, positive pressure respirator or other known devices and. . .

DETDESC:

DETD(13)

In this study we have focused on shorttime effects on coagulation parameters in rabbits from inhaled **nitric** **oxide** (NO) in the dose range 3-300 ppm, and in three human subjects exposed to 30 ppm NO. The studies were. . .

DETDESC:

DETD(20)

The Human Ethics Committee of Uppsala University has approved studies on shortterm (<30 minutes) exposure with inhaled **nitric** **oxide** 80 ppm NO or less in human volunteers. The subjects were studied at least 2 hours after a light meal,. . .

DETDESC:

DETD(34)

This study confirms that inhalation of **nitric** **oxide** prolongs the bleeding time in rabbits and humans. The prolongation of bleeding time was significant after 15 minutes of inhalation. . .

DETDESC:

DETD(40)

3. Hogman M, Frostell C, Arnberg H, Hedenstierna G. Inhalation of **nitric** **oxide** modulates metacholine-induced bronchoconstriction in the rabbit. Eur Respir J 1993; 6:177-180.

DETDESC:

DETD(43)

The Human Ethics Committee of the Karolinska Institute has approved the use of **nitric** **oxide** inhalation in patients with critical pulmonary hypertension. For details of equipment see appendix.

DETDESC:

DETD(47)

Inhalation of **nitric** **oxide**

DETDESC:

DETD(72)

These data establish that inhaled NO gas results in accumulation of a pool or reservoir of **nitric** **oxide** plasma (blood) S-nitrosoprotein in the systemic bloodstream upon inhalation administration of NO.

CLAIMS:

CLMS(1)

What . . .

an amount of a compound effective for systemically inhibiting blood platelet aggregation and coagulation selected from the group consisting of **nitric** **oxide** and a compound that delivers **nitric** **oxide**.

CLAIMS:

CLMS(2)

2. The method of claim 1 wherein the **nitric** **oxide** delivering compound is selected from the group of S-nitrosothiols, S-nitroso-proteins, NONOnates, iron nitrosyls, iron nitrosyls with thiolate ligands, thionitrites, thionitrates,. . .

CLAIMS:

CLMS(3)

3. . . . which comprises a compound effective for treating acute respiratory distress syndrome in said patient selected from the group consisting of **nitric** **oxide** and a compound that delivers **nitric** **oxide**.

CLAIMS:

CLMS(4)

4. The method of claim 3 wherein the **nitric** **oxide** delivering compound is selected from the group of S-nitrosothiols; S-nitroso-proteins, NONOnates, iron nitrosyls, iron nitrosyls with thiolate ligands, thionitrites, thionitrates,. . .

CLAIMS:

CLMS(5)

5. A method for establishing an increased level of **nitric** **oxide** in the systemic circulation of a patient in need thereof comprising administering by the inhalation route to the lung of. . . in need thereof an amount of a pharmaceutical composition which comprises a compound effective for establishing an increased level of **nitric** **oxide** in the systemic circulation of said patient selected from the group consisting of **nitric** **oxide** and a compound that delivers **nitric** **oxide**.

CLAIMS:

CLMS(6)

6. The method of claim 5 wherein the **nitric** **oxide** delivering compound is selected from the group of S-nitrosothiols, S-nitroso-proteins, NONOnates, iron nitrosyls, iron nitrosyls with thiolate ligands, thionitrites, thionitrates,. . .
=

=> d l5 16,17,21 kwic

US PAT NO: 5,427,797 [IMAGE AVAILABLE] L5: 16 of 24
TITLE: Systemic effects of nitric oxide **inhalation**

ABSTRACT:
Nitric oxide or nitric oxide releasing or delivering compounds administered by the **inhalation** route to humans and animals in need thereof have a systemic and pulmonary effect of preventing or treating blood platelet. . .

SUMMARY:

BSUM(3)

The consequences of NO production in the **lung** are not known. However, it has been believed that potential beneficial bronchodilation effects of NO may be counterbalanced by generation. . . For example, the reaction between NO.sup..multidot., and O.sub.2 or reactive O.sub.2 species which are present in high concentrations in the **lung**, generates highly toxic products, such as NO.sub.2 and peroxynitrite. These reactions also result in the rapid inactivation of NO, thus. . .

SUMMARY:

BSUM(4)

Nonetheless, . . . WO 92/10228 discloses a method for treating or preventing bronchoconstriction, e.g., asthma or reversible pulmonary vasoconstriction, e.g., pulmonary hypertension, by **inhalation** of gaseous nitric oxide or nitric oxide-releasing compounds. Many such compounds are known. These investigators characterize the mammalian circulatory system. . . report that (since NO gas which enters the bloodstream is rapidly inactivated by combination with hemoglobin) the bronchodilatory effects of **inhaled** NO are limited to the ventilated bronchi and the vasodilatory effects of **inhaled** NO are limited to those blood vessels near the site of NO passage into the blood stream: i.e., pulmonary microvessels.. . . systemic vasodilation. More specifically, they report that the rapid binding of NO to hemoglobin ensures that any vasodilatory action of **inhaled** NO is solely a local or selective effect in the blood vessels of the **lung**, with no concomitant vasodilation downstream in the systemic circulation.

SUMMARY:

BSUM(6)

In . . . the first time that nitric oxide and its adducts, conjugates and other nitric oxide containing compounds widen administered by the **inhalation** route to an individual in need thereof, as the compound per se or as part of an adduct, conjugate or. . .

DRAWING DESC:

DRWD(2)

FIG. . . . NO (n=2), 30 ppm NO (n=7) or 300 ppm NO (n=2) for 15 minutes, and 15 minutes after terminating NO **inhalation**. Bleeding time ratio in parenthesis, the actual bleeding time divided with the baseline value.

DETDESC:

DETD(2)

Thus, . . . of both systemic and pulmonary emboli, for preventing and reversing platelet aggregation and for anticoagulant therapy comprising administering by the **inhalation** route to a human or animal in need thereof a therapeutically effective amount of a compound (or pharmaceutical composition comprising. . .

DETDESC:

DETD(3)

Another . . . to a method for the prevention or treatment of angina pectoris and other unstable coronary syndromes comprising administering by the **inhalation** route to a human or animal in need thereof a therapeutically effective amount of a compound (or pharmaceutical composition comprising. . .

DETDESC:

DETD(4)

Another aspect relates to a method for the prevention or treatment of acute respiratory distress syndrome (ARDS) comprising administering by the **inhalation** route to an animal in need thereof a therapeutically effective amount of a compound (or pharmaceutical composition comprising such a. . .

DETDESC:

DETD(9)

Administration of the nitric oxide or nitric oxide releasing agent to the **lung** can be by hand held, portable ventilator, positive pressure respirator or other known devices and methods for respiratory administration.

DETDESC:

DETD(12)

Effect of NO **Inhalation** on Coagulation Time Rabbit and Human

DETDESC:

DETD(13)

In this study we have focused on shorttime effects on coagulation parameters in rabbits from **inhaled** nitric oxide (NO) in the dose range 3-300 ppm, and in three human subjects exposed to 30 ppm NO. The. . .

DETDESC:

DETD(16)

The . . . fraction (FIO.sub.2) of 0.3. After a 30 minutes stabilization period a double tidal volume was delivered to reopen any collapsed **lung** tissue. An inflation pressure (Pmax) limit was set at 25 cm H.sub.2 O. Respiratory mechanics, i.e. respiratory resistance (Rrs) and **lung** compliance (Crs), mean arterial pressure (MAP), heart rate, end-tidal CO.sub.2 (EtCO.sub.2) and peripheral oxygen saturation (SpO.sub.2) were obtained at baseline and at the end of the NO **inhalation** period. NO 1000 parts per million (ppm) in nitrogen (N.sub.2) was obtained from AGA Medical Gas AS, Lidingo, Sweden. The. . .

DETDESC:

DETD(18)

Our protocol was to measure bleeding time and sample blood at 1) baseline; 2) after 15 minutes of **inhaling** NO 3 ppm (n=2), NO 30 ppm (n=7), or NO 300 ppm (n=2); 3) after 30 minutes from terminating NO **inhalation**. The measurement during NO **inhalation** was begun after 15 minutes and NO **inhalation** continued until the measurement was completed.

DETDESC:

DETD(20)

The Human Ethics Committee of Uppsala University has approved studies on shortterm (<30 minutes) exposure with **inhaled** nitric oxide 80 ppm NO or less in human volunteers. The subjects were studied at least 2 hours after a light meal, were subjectively **lung** healthy and studied awake sitting in a chair. They were presently taking no medication and had not been taking aspirin. . .

DETDESC:

DETD(21)

The . . . one-way valve and a soda lime cannister which removed the NO.sub.2 formed in the system, and the gas was then **inhaled** through a mouth piece. NO 1000 ppm in N.sub.2 was mixed with N.sub.2 and O.sub.2 using volumetrically calibrated flowmeters, to. . .

DETDESC:

DETD(23)

Our protocol was to measure bleeding time and sample blood at 1) baseline; 2) after 15 minutes of **inhaling** NO 30 ppm; and 3) after 60 minutes from terminating NO **inhalation**. NO **inhalation** was continued until the measurement of bleeding time was completed.

DETDESC:

DETD(28)

The . . . the study (data not shown). Bleeding time was 49.+-.6 seconds during baseline conditions and increased after 15 minutes of NO **inhalation** 30 ppm to 72.+-.9 seconds (ratio 1.54 .+-.0.2, p=0.015). Finally, 30 minutes after terminating NO **inhalation** the bleeding time was 53.+-.4 seconds (ratio 1.13 .+-.0.2). The two rabbits exposed to only 3 ppm NO increased their mean bleeding time ratio to 1.48 and then returned to baseline 30 minutes after terminating NO. **Inhalation** of 300 ppm NO in two rabbits increased the bleeding time ratio to 2.44, which remained high 30 minutes after. . .

DETDESC:

DETD(30)

No discomfort was experienced by any subject during NO **inhalation**. There were no change in heart rate or SpO.sub.2 during the study. There were no significant alterations in platelet count,. . . to mean 1.4 after 15 minutes of breathing NO 30 ppm, and returned towards baseline 60 minutes after terminating NO **inhalation**. See also Table 1.

DETDESC:

DETD(32)

Bleeding time in seconds before, during NO **inhalation** after 15 minutes of **inhaling** 30 ppm NO, and 60 minutes after terminating NO **inhalation**. Bleeding time ratio in parenthesis, the actual bleeding time divided with the baseline value.

DETDESC:

DETD(34)

This study confirms that **inhalation** of nitric oxide prolongs the bleeding time in rabbits and humans. The prolongation of bleeding time was significant after 15 minutes of **inhalation** of 30 ppm NO in rabbits, and could be clearly demonstrated in human volunteers at the same dose for the. . .

DETDESC:

DETD(36)

When platelets pass the pulmonary circulation they could vary well absorb some of tile **inhaled** NO, and in this way have the aggregation and adhesion tendency somewhat supressed by an increase of cyclic GMP content in these platelets (4). The observation in this study of a prolonged (>30 minutes) effect of NO **inhalation** when inspiring 300 ppm NO necessitates an additional mechanism for the effect. **Inhalation** of NO must increase a pool of NO or NO releasing compounds in blood, that can release NO slowly for many minutes after NO **inhalation** has been stopped.

DETDESC:

DETD(40)

3. Hogman M, Frostell C, Arnberg H, Hedenstierna G. **Inhalation** of nitric oxide modulates metacholine-induced bronchoconstriction in the rabbit. Eur Respir J 1993; 6:177-180.

DETDESC:

DETD(43)

The Human Ethics Committee of the Karolinska Institute has approved the use of nitric oxide **inhalation** in patients with critical pulmonary hypertension. For details of equipment see appendix.

DETDESC:

DETD(47)

Inhalation of nitric oxide

DETDESC:

DETD(48)

Since . . . circulatory collapse was deemed imminent a decision was made to attempt to restore gas exchange with the addition of NO **inhalation**. No 20 ppm was added to inspred gas and 40 ml of Tris-sdiumbicarbonate buffer solution (Tribonate, Pharmacia, Uppsala, Sweden) was. . .

DETDESC:

DETD(51)

The first attempt to discontinue NO **inhalation** was performed 40 hours after initiating this treatment. At this point electrolyte and acid-base disorders had been corrected and the. . . ductus arteriosus had closed. No alterations in gas exchange or echocardiographic parameters appeared within 15 minutes after discontinuation of NO **inhalation**. Since significant pulmonary hypertension was still evident it was decided to continue NO **inhalation** for another 12 hours. During this period it was possible to further reduce FlO.sub.2 to 0.21. As no deterioration in. . .

DETDESC:

DETD(55)

(a) Plasma levels of S-nitrosoprotein were 5.9 .mu.m after 30 min of **inhaled** NO gas 5 ppm.

DETDESC:

DETD(56)

(b) Plasma levels of S-nitrosoprotein fell after discontinuation of **inhaled** NO; levels were 5.3 .mu.m 30 minutes after discontinuing NO.

DETDESC:

DETD(58)

These data establish that **inhaled** NO gas results in a pool or reservoir of plasma (blood) S-nitrosoprotein that decreases over time after NO administration is. . .

DETDESC:

DETD(69)

Time dependent increase in plasma S-nitrosoproteins before **inhaled** NO

DETDESC:

DETD(70)

(a) before **inhaled** NO gas plasma level=2.5 .mu.m

DETDESC:

DETD(71)

(b) after **inhaled** NO gas, plasma level=3.46 .mu.m

DETDESC:

DETD(72)

These data establish that **inhaled** NO gas results in accumulation of a pool or reservoir of nitric oxide plasma (blood) S-nitrosoprotein in the systemic bloodstream upon **inhalation** administration of NO.

CLAIMS:

CLMS(1)

What . . .

blood platelet aggregation and coagulation comprising systemically treating a patient for blood platelet aggregation and coagulation by administering by the **inhalation** route to the **lung** of a patient in need thereof an amount of a compound effective for systemically inhibiting blood platelet aggregation and coagulation. . .

CLAIMS:

CLMS(3)

3. A method for treating acute respiratory distress syndrome in a patient in need thereof comprising administering to the **lung** of a patient suffering from acute respiratory distress syndrome an amount of a pharmaceutical composition which comprises a compound effective. . .

CLAIMS:

CLMS(5)

5. . . . an increased level of nitric oxide in the systemic circulation of a patient in need thereof comprising administering by the **inhalation** route to the **lung** of said patient in need thereof an amount of a pharmaceutical composition which comprises a compound effective for establishing an. . .

US PAT NO: 5,426,122 [IMAGE AVAILABLE] L5: 17 of 24

SUMMARY:

BSUM(9)

The . . . with age (J. Biol. Chem. 75:789-794 (1927)). In contrast, Leslie et al. showed an increase in rat brain, liver, spleen, **lung** and femur silicon with age (Proc. Soc. Exptl. Bio. Med. 110:218 (1962)). And Kworning et al. described elevated silicon deposition. . .

SUMMARY:

BSUM(11)

Much information is known about the toxic effects of silicon in the **lung**. Varying amounts of silica normally enter the respiratory tract across the **lung** barrier as silicic acid and are eventually eliminated. Prolonged **inhalation** and accumulation of fine particulate silica in the **lung**, however, produces a pulmonary inflammatory response, granuloma formation and chronic fibrosis (silicosis) (Prin. Int. Med., 9th Ed., Isselbacher et al.. . .

DETDESC:

DETD(3)

While . . . (1990)). Superoxide dismutase reduces the levels of oxygen free radicals (or reactive oxygen metabolites) which can cause cell damage. The **lung**, brain, kidney and red blood cells contain many compounds which are especially sensitive to oxygen free radical damage, such as phospholipids of brain myelin, **lung** surfactant, and red blood cells' lipid membranes and hemoglobin. The presence of excessive silicon concentration both induces oxygen free radical. . .

US PAT NO: 5,380,758 [IMAGE AVAILABLE] L5: 21 of 24

SUMMARY:

BSUM(9)

Pulmonary . . . believed to induce nitric oxide synthetase, thus serving as a source of NO. The consequences of NO production in the **lung** are not known. However, the potential beneficial effects of NO through bronchodilation may be counterbalanced by generation of toxic nitrogen. . .

SUMMARY:

BSUM(10)

Likewise, . . . For example, the reaction between NO., and O.sub.2 or reactive O.sub.2 species which are present in high concentrations in the **lung**, generates highly toxic products, such as NO.sub.2 and peroxynitrite. These reactions also result in the rapid inactivation of NO, thus. . .

SUMMARY:

BSUM(40)

The . . . prevention of respiratory disorders by administering a therapeutically effective amount of S-nitrosothiol compound to an animal. Respiratory disorders include obstructive **lung** disease, emphysema, asthma, bronchitis, fibrosis, excessive mucus secretion, obstruction or air flow, and **lung** disorders resulting from post-surgical complications.

DETDESC:

DETD(8)

The term "respiratory disorder" refers to any impairment of **lung** function which involves constriction of airways and changes in blood gas levels or **lung** function.

DETDESC:

DETD(9)

For example, airway obstruction constitutes a respiratory disorder which occurs as a result of acute pulmonary impairment or obstructive **lung** disease. Severe airway obstruction may ultimately result in life-threatening respiratory failure. Airway obstruction occurs in patients with chronic obstructive **lung** diseases, such as emphysema and bronchitis. These patients often experience recurrent episodes of respiratory failure as a result of severe. . .

DETDESC:

DETD(11)

Another obstructive **lung** disease, cystic fibrosis, results from abnormal exocrine gland function. Clinical manifestations include excessive mucous secretion, hypertrophy of bronchial glands, infection,. . .

DETDESC:

DETD(13)

A . . . to remove secretions and reverse airway constriction. The most commonly used bronchodilatory agents are beta-agonists, such as isoproterenol, given by **inhalation** or subcutaneous injection, and methylxanthines, such as theophylline, given orally or by infusion.

DETDESC:

DETD(27)

In . . . in which a flexible fiberoptic, or rigid bronchoscope is introduced into the tracheobronchial tree for the purpose of bronchial visualization, **lung** biopsy or brushings, aspiration of secretions, and delivery of pharmacological agents.

DETDESC:

DETD(65)

Male Hartley guinea pigs (500-600 g) were anesthetized by **inhalation** of enflurane to achieve a surgical plane of anesthesia. The trachea were excised and placed in Kreb's-Henseleit buffer (mM): NaCl. . .

DETDESC:

DETD(102)

The results also suggests that, in addition to the primary site of obstruction in the **lung**, the efficacy of nitro(so)-bronchodilators may be determined by the nature of the chemical mediators contributing to bronchoconstriction. In particular, S-nitrosothiols. . .

CLAIMS:

CLMS(7)

7. The method of claim 4 wherein said respiratory disorder is obstructive **lung** disease selected from the group consisting of emphysema, asthma bronchitis, fibrosis, excessive mucous secretion, obstruction of air flow, and **lung** disorders resulting from post-surgical complications.
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=> d l5 16,17 21 cit

16. 5,427,797, Jun. 27, 1995, Systemic effects of nitric oxide **inhalation**; Claes G. Frostell, et al., 424/434, 44, 45; 514/826, 957 [IMAGE AVAILABLE]

17. 5,426,122, Jun. 20, 1995, Methods for reducing blood pressure with dimercaptosuccinic acid (DMSA); Harvey C. Gonick, et al., 514/578 [IMAGE AVAILABLE]

21. 5,380,758, Jan. 10, 1995, S-nitrosothiols as smooth muscle relaxants and therapeutic uses thereof; Jonathan Stamler, et al., 514/562 [IMAGE AVAILABLE]
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